contd. a3

(5*R*)-1-[9-chloro-5-ethyl-5-hydroxy-10-methyl-3,15-dioxo-4,5,13,15-tetrahydro-1H,3H-oxepino[3',4:6,7]indolizino[1,2-b]quinolin-12-yl-methyl]-4-methyl-hexahydropyridium chloride;

(5*R*)-5-ethyl=9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1H,3H-oxepino[3'4':6,7]indolizino[1,2-b]quinoline-3,15-dione; and

(5*R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1H,3H-oxepino[3'4':6,7]indolizino[1,2-b]quinoline-3,15-dione; and a pharmaceutically acceptable salt thereof.

REMARKS

The amendment is submitted to insert reference to the parent applications and their status, to remove multiple dependency from the claims and to conform the claims to the American practice.

Respectfully submitted,
BIERMAN, MUSERLIAN AND LUCAS

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Enclosures: Marked-Up Version of Specification and Claims
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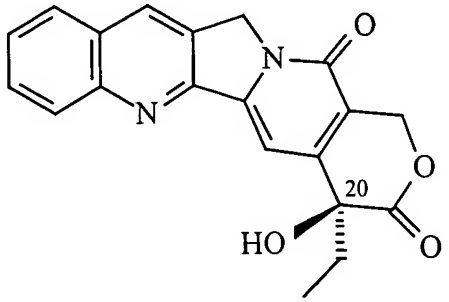
MARKED-UP VERSION OF SPECIFICAT

New analogues of camptothecin, their use as medicaments and the pharmaceutical compositions containing them

See insert "A"

Camptothecin is a natural compound which has been isolated for the first time from the leaves and the bark of the Chinese plant called *camptotheca acuminata* (see Wall et al. J. Amer. Chem. Soc. 88:3888 (1966)). Camptothecin is a pentacyclic compound constituted by an indolizino[1,2-b]quinoline fragment fused with an α-hydroxylactone with six members. The carbon in position 20 which carries the α-hydroxy group is asymmetrical and confers a rotatory power on the molecule. The natural form of camptothecin has an absolute "S" configuration as regards the carbon 20 and corresponds to the following formula:



Camptothecin has an anti-proliferative activity in several cancerous cell lines, including the cell lines of human tumors of the colon, lung and breast (Suffness, M et al: The Alkaloids Chemistry and Pharmacology, Bross A., ed., Vol. 25, p. 73 (Acedemic Press, 1985)). It is suggested that the anti-proliferative activity of camptothecin is related to its inhibitory activity on DNA topoisomerase I.

It has been indicated that α-hydroxylactone was an absolute requirement both for the *in vivo* and *in vitro* activity of campotothecin (Camptothecins: New Anticancer Agents, Putmesil, M et al, ed., p. 27 (CRC Press, 1995); Wall M. et al, Cancer Res. 55:753 (1995); Hertzberg et al, J. Med. Chem. 32:715 (1982) and Crow et al, J. Med. Chem. 35:4160 (1992)). The present invention relates to a new class of compounds of camptothecin, in which a β-hydroxylactone replaces the natural α-hydroxylactone of camptothecin. The compounds according to the present invention present a powerful biological activity which is unexpected with regard to the state of the prior art.

Therefore a subject of the invention is new analogues of camptothecin which differ from all known derivatives of camptothecin in the sense that they contain β-hydroxylactone (or its open hydroxycarboxylic form) instead of an α-hydroxylactone (or its open hydroxycarboxylic form); or a pharmaceutically acceptable salt of one of

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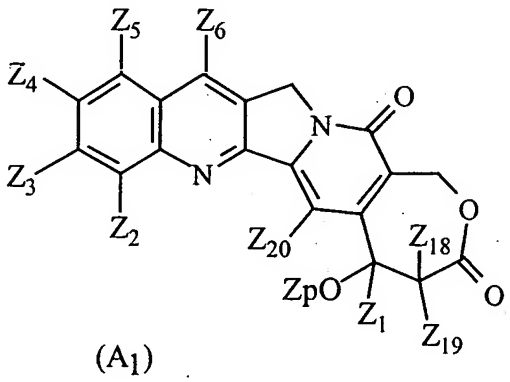
INSERT "A"

--**PRIOR APPLICATIONS**

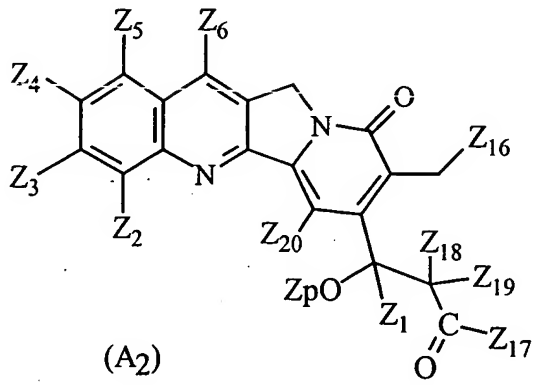
This application is a Continuation-in-Part of U.S. Patent Application Serial No. 09/332,520 filed June 14, 1999 which is a Continuation-in-Part of U.S. Patent Application Serial No. 973,561 filed December 2, 1997, now U.S. Patent No. 5,981,542 which is a 371 of PCT/FR96/00980 filed June 21, 1996 and a Continuation-in Part of U.S. Patent Application Serial No. 09/806,952 filed April 5, 2001 which is a 371 of PCT/FR00/00461 filed February 24, 2000.--

MARKED-UP VERSION OF
CLAIMS

1. Compounds of general formula (A1) or (A2)



(A1)



(A2)

in racemic or enantiomeric form or any combinations of these forms, in which

Z_1 represents a lower alkyl, a lower alkenyl, a lower alkynyl, a lower haloalkyl, a lower alkoxy lower alkyl or lower alkylthio lower alkyl;

Z_2, Z_3, Z_4, Z_5 and Z_6 represent, independently,

i) H, halo, lower haloalkyl, alkyl containing 1 to 12 carbon atoms optionnally substituted by one or more halo radicals indentical or different, lower alkenyl, cycloalkyl, cycloalkyl lower alkyl, cyano, lower cyanoalkyl, nitro, lower nitroalkyl, amido, lower amidoalkyl, hydrazino, lower hydrazinoalkyl, azido, lower azidoalkyl, lower alkyl lower sulphonylalkyl, $-(CH_2)_mNZ'_6Z'_7$, $-(CH_2)_mOZ'_6$, $-(CH_2)_mSZ'_6$, $-(CH_2)_mCO_2Z'_6$, $-(CH_2)_mNZ'_6C(O)Z_8$, $-(CH_2)_mC(O)Z_8$, $-(CH_2)_mOC(O)Z_8$, $-O(CH_2)_mNZ'_6Z'_7$, $-OC(O)NZ'_6Z'_7$, $-OC(O)(CH_2)_mCO_2Z'_6$, $-OSO_2Z_7$, $-(CH_2)_mN(CH_3)(CH_2)_nNZ'_6Z'_7$, $-(CH_2)_mOC(O)NZ'_6Z'_7$, $-(CH_2)_mS(O)_qZ_{11}$, $-(CH_2)_mP(O)Z_{12}Z_{13}$, $-(CH_2)_2P(S)Z_{12}Z_{13}$, $-(CH_2)_mSiZ'_{11}Z'_{12}Z'_{13}$; or ii) $-(CH_2)_n[N=X]$, $-OC(O)[N=X]$, $-(CH_2)_mOC(O)[N=X]$, aryl or lower arylalkyl, each unsubstituted or substituted (i.e. substituted between once and four times on the aryl group or the heterocycle) or non-substituted in which the substituent is a lower alkyl, lower arylalkyl, halo, hydroxy, $-OCF_3$, nitro, amino, lower alkylamino, di(lower alkyl)amino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy or lower alkoxy lower alkyl or iii) Z_3 and Z_4 or Z_4 and Z_5 form together a chain with 3 or 4 members in which the elements of the chain are selected from the group constituted by CH, CH_2, O, S, N or NZ_9;

Z_7 represents a lower alkyl radical optionally substituted by one or more halo radicals identical or different, or an aryl optionally susbtituted by one or more lower alkyl radicals identical or different ;

Z'_6 and Z'_7 represent, independently, i) H, a lower alkyl, lower hydroxyalkyl, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy lower alkyl, lower haloalkyl, or ii) aryl or lower arylalkyl, each substituted (i.e. substituted between once and four times on the aryl group) or non substituted in which the substituent is a lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy or lower alkoxy lower alkyl ;

Z_8 represents i) H, a lower alkyl, lower hydroxyalkyl, amino, lower alkylamino, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy, lower alkoxy lower alkyl, lower haloalkyl, or ii) aryl or lower arylalkyl, each substituted (i.e. substituted between once and four times on the aryl group) or non substituted, in which the substituent is a lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy or lower alkoxy lower alkyl;

Z_9 represents i) H, a lower alkyl, lower haloalkyl, or ii) aryl or lower arylalkyl, each substituted or non substituted in which the substituent is lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy or lower alkoxy lower alkyl;

Z_{10} represents i) H, a lower alkyl, lower haloalkyl, lower alkoxy, or ii) aryl substituted (i.e. having one to four substituents on the aryl group)or non substituted in which the substitutent is lower alkyl, lower haloalkyl, lower hydroxyalkyl or lower alkoxy lower alkyl;

Z_{11} represents a lower alkyl, aryl, $-(CH_2)_mOZ_{14}$, $-(CH_2)_mSZ_{14}$, $-(CH_2)_2NZ_{14}Z_{15}$ or $-(CH_2)_m[N=X]$;

Z_{12} and Z_{13} represent, independently, a lower alkyl, aryl, lower alkoxy, aryloxy or amino;

Z'_{11}, Z'_{12} and Z'_{13} represent, independently, H or a lower alkyl radical ;

Z_{14} and Z_{15} represent, independently, H, lower alkyl or aryl;

Z_{16} represents H or $-OZ_{21}$;

Z_{17} represents $-OZ'_6$ or $-NZ'_6Z'_7$;

Z_{18} and Z_{19} represent, independently, H, halo, lower alkyl, lower alkoxy or hydroxy;

Z_{20} represents H or halo;

Z_{21} represents H, a lower alkyl, -CHO or -$C(O)(CH_2)_mCH_3$;

Z_p represents H or an easily cleavable group preferably chosen from the groups corresponding to the formula -C(O)-A-$NZ_{22}Z_{23}$, in which A represents a linear or branched alkylene radical optionally substituted by a radical chosen from the free, esterified or salified hydroxy, halogen, free, esterified or salified carboxy, amino, mono- or dialkylamino radicals;

Z_{22} and Z_{23} represent, independently, H, a lower alkyl, lower hydroxyalkyl, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy lower alkyl, lower haloalkyl, or substituted or non substituted aryl or lower arylalkyl (e.g., substituted one to four times on the aryl group), in which the substituent is a lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy or lower alkoxy lower alkyl;

m is an integer comprised between 0 and 6;

n is 1 or 2; and

q represents an integer from 0 to 2; and

[N=X] represents a heterocyclic group with 4 to 7 members with the nitrogen atom which is a member of the heterocyclic ring, and X representing the chain necessary to complete said heterocyclic group and selected from the group constituted by O, S, CH_2, CH, N, NZ_9 and $C(O)Z_{10}$;

or pharmaceutically acceptable salts of thereof.

2. Compounds of general formula (A_1) or (A_2) as claimed in claim 1, in racemic or enantiomeric form or any combinations of these forms, characterized in that

Z_1 represents a lower alkyl, a lower alkenyl, a lower alkynyl, a lower haloalkyl, a lower alkoxy lower alkyl or lower alkylthio lower alkyl;

Z_2 represents H, halo or -OSO_2Z_7;

Z_3, Z_4 and Z_5 represent, independently, i) H, halo, lower haloalkyl, lower alkyl, lower alkenyl, cyano, lower cyanoalkyl, nitro, lower nitroalkyl, amido, lower amidoalkyl, hydrazino, lower hydrazinoalkyl, azido, lower azidoalkyl, -$(CH_2)_mNZ'_6Z'_7$, -$(CH_2)_mOZ'_6$, -$(CH_2)_mSZ'_6$, -$(CH_2)_mCO_2Z'_6$, -$(CH_2)_mNZ'_6C(O)Z_8$, -$(CH_2)_mC(O)Z_8$, -$(CH_2)_mOC(O)Z_8$, -$O(CH_2)_mNZ'_6Z'_7$, -$OC(O)NZ'_6Z'_7$, -$OC(O)(CH_2)_mCO_2Z'_6$, -OSO_2Z_7 or ii) -$(CH_2)_n$[N=X], -OC(O)[N=X], -$(CH_2)_m$OC(O)[N=X] (in which [N=X], in this invention, represents a heterocyclic group with 4 to 7 members with the nitrogen atom N, which is a member of the heterocyclic group, and X represents the remaining members, which are

necessary to complete the heterocylic group, selected from the group ~~constituted by~~ O, S, CH_2, CH, N, NZ_9 and COZ_{10}, aryl or lower arylalkyl, ~~each~~ substituted ~~(i.e. substituted between once and four times on the aryl group or the heterocycle) or non substituted in which the substituent is a~~ lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy ~~or~~ lower alkoxy lower alkyl or **iii)** Z_3 and Z_4 or Z_4 and Z_5 form together a chain with 3 or 4 ~~members~~ in which the elements of the chain are selected from the group ~~constituted by~~ CH, CH_2, O, S, N ~~or~~ NZ_9;

Z_6 ~~represents~~ **i)** H, halo, lower haloalkyl, alkyl containing 1 to 12 carbon atoms ~~optionnally~~ substituted by ~~or more~~ halo ~~radicals indentical or different~~, lower alkoxy, lower alkoxy lower alkyl, lower alkylthio lower alkyl, cycloalkyl, cycloalkyl lower alkyl, cyano, cyanoalkyl, lower alkyl lower sulphonylalkyl, lower hydroxyalkyl, nitro, $-(CH_2)_mC(O)Z_8$, $-(CH_2)_mNZ'_6C(O)Z_8$, $-(CH_2)_mNZ'_6Z'_7$, $-(CH_2)_mN(CH_3)(CH_2)_nNZ'_6Z'_7$, $-(CH_2)_mOC(O)Z_8$, $-(CH_2)_mOC(O)NZ'_6Z'_7$, $-(CH_2)_mS(O)_qZ_{11}$, $-(CH_2)_mP(O)Z_{12}Z_{13}$, $-(CH_2)_2P(S)Z_{12}Z_{13}$, $-(CH_2)_mSiZ'_{11}Z'_{12}Z'_{13}$; or **ii)** $-(CH_2)_n[N=X]$, $-OC(O)[N=X]$, $-(CH_2)_mOC(O)[N=X]$, each substituted ~~(i.e. substituted between once and four times on the heteroaryl group) or non substituted in which the substituent is a~~ lower alkyl, lower arylalkyl, halo, hydroxy, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy ~~or~~ lower alkoxy lower alkyl; or **iii)** aryl or lower arylalkyl, each substituted ~~(i.e. substituted between once and four times on the aryl group) or non substituted in which the substituent is a~~ lower alkyl, halo, hydroxy, nitro, $-OCF_3$, amino, lower alkylamino, di(lower alkyl)amino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy ~~or~~ lower alkoxy lower alkyl ;

Z_7 ~~represents a~~ lower alkyl ~~radical optionnally~~ substituted by ~~or more~~ halo ~~radicals identical or different~~, or ~~an~~ aryl ~~optionnally~~ susbtituted by ~~or more~~ lower alkyl ~~radicals identical or different~~ ;

Z'_6 and Z'_7 ~~represent~~, independently ~~i)~~ H, a lower alkyl, lower hydroxyalkyl, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy lower alkyl, lower haloalkyl, or **ii)** aryl or lower arylalkyl, ~~each~~ substituted ~~(i.e. substituted between once and four times on the aryl group) or non substituted in which the substituent is a~~ lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy ~~or~~ lower alkoxy lower alkyl ;

Z_8 represents i) H, a lower alkyl, lower hydroxyalkyl, amino, lower alkylamino, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy, lower alkoxy lower alkyl, lower haloalkyl, or ii) aryl or lower arylalkyl, each substituted (i.e. substituted between once and four times on the aryl group) or non substituted, in which the substituent is a lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy or lower alkoxy lower alkyl;

Z_9 represents i) H, a lower alkyl, lower haloalkyl, or ii) aryl or lower arylalkyl, each substituted or non substituted in which the substituent is lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy or lower alkoxy lower alkyl;

Z_{10} represents i) H, a lower alkyl, lower haloalkyl, lower alkoxy, or ii) aryl substituted (i.e. having one to four substituents on the aryl group) or non substituted in which the substituent is lower alkyl, lower haloalkyl, lower hydroxyalkyl or lower alkoxy lower alkyl;

Z_{11} represents a lower alkyl, aryl, $-(CH_2)_mOZ_{14}$, $-(CH_2)_mSZ_{14}$, $-(CH_2)_2NZ_{14}Z_{15}$ or $-(CH_2)_m[N=X]$;

Z_{12} and Z_{13} represent, independently, a lower alkyl, aryl, lower alkoxy, aryloxy or amino;

Z'_{11}, Z'_{12} and Z'_{13} represent, independently, H or a lower alkyl radical ;

Z_{14} and Z_{15} represent, independently, H, lower alkyl or aryl;

Z_{16} represents H or $-OZ_{21}$;

Z_{17} represents $-OZ'_6$ or $-NZ'_6Z'_7$;

Z_{18} and Z_{19} represent, independently, H, halo, lower alkyl, lower alkoxy or hydroxy;

Z_{20} represents H or halo;

Z_{21} represents H, a lower alkyl, -CHO or $-C(O)(CH_2)_mCH_3$;

Z_p represents H or an easily cleavable group preferably chosen from the groups corresponding to the formula $-C(O)-A-NZ_{22}Z_{23}$, in which A represents a linear or branched alkylene radical optionally substituted by a radical chosen from the free, esterified or salified hydroxy, halogen, free, esterified or salified carboxy, amino, mono or dialkylamino radicals ;

Z_{22} and Z_{23} represent, independently, H, a lower alkyl, lower hydroxyalkyl, lower alkyl lower aminoalkyl, lower aminoalkyl, cycloalkyl, cycloalkyl lower alkyl, lower alkenyl, lower alkoxy lower alkyl, lower haloalkyl, or ii) substituted or non substituted aryl or lower arylalkyl (i.e. substituted by 1 to 4

members of the group consisting of
~~one to four times on the aryl group), in which the substituent is a~~ lower alkyl, halo, nitro, amino, lower alkylamino, lower haloalkyl, lower hydroxyalkyl, lower alkoxy ~~or~~ and lower alkoxy lower alkyl;

m is an integer ~~comprised~~ between 0 and 6;

n is 1 or 2; and

q ~~represents~~ is an integer from 0 to 2; and

[N=X] ~~represents~~ is a heterocyclic group with 4 to 7 ring members with the nitrogen atom which is a member of the heterocyclic ring, and X ~~representing~~ is the chain necessary to complete said heterocyclic group and selected from the group ~~constituted by~~ consisting of O, S, CH_2, CH, N, NZ_9 and COZ_{10} ;

or a pharmaceutically acceptable salts ~~of~~ thereof.

3. Compounds ~~as claimed in~~ of claim 1 ~~or 2, characterized in that~~ wherein Z_2 ~~represents~~ is H or halo and/or pharmaceutically acceptable salts ~~of~~ thereof.

4. Compounds ~~as claimed in~~ of claim 1 ~~or 2, characterized in that~~ wherein Z_3 ~~represents~~ is halo ; ~~or~~ and/or pharmaceutically acceptable salts ~~of~~ thereof.

5. Compounds ~~as claimed in any~~ of claims 1 ~~to 4, characterized in that~~ wherein

Z_1 ~~represents a~~ is a lower alkyl ;

Z_2 ~~represents~~ is H or halo ;

Z_3, Z_4 and Z_5 ~~represent~~ are, independently, **i)** H, halo, lower alkyl, $-(CH_2)_mNZ'_6Z'_7$, $-(CH_2)_mOZ'_6$ and $-OSO_2Z_7$ or **ii)** $-(CH_2)_n[N=X]$ or **iii)** Z_3 and Z_4 or Z_4 and Z_5 form together a chain with 3 or 4 members in which the elements of the chain are selected from the group ~~constituted by~~ consisting of CH, CH_2, O, S, N and/or NZ_9;

Z_6 is **i)** ~~represents~~ H, halo, alkyl ~~containing~~ of 1 to 12 carbon atoms ~~optionnally~~ unsubstituted or substituted by at least one ~~or more~~ halo ~~radicals indentical or different,~~ lower alkoxy lower alkyl, cycloalkyl, cycloalkyl lower alkyl, lower hydroxyalkyl, $-(CH_2)_mNZ'_6Z'_7$ and $-(CH_2)mSiZ'_{11}Z'_{12}Z'_{13}$; or **ii)** $-(CH_2)_n[N=X]$ unsubstituted or ~~non~~ substituted ~~in which the substituent is~~ with a lower alkyl or lower arylalkyl or **iii)** aryl or lower arylalkyl, ~~each~~ unsubstituted or substituted or ~~non~~ substituted ~~in which the substituent is a~~ lower alkyl, halo, $-OCF_3$, di(lower alkyl)amino and/or lower haloalkyl ;

Z_7 is ~~represents a~~ lower alkyl ~~radical optionnally~~ unsubstituted or substituted by at least one ~~or more~~ halo ~~radicals identical or different~~ ;

Z'_6 and Z'_7 ~~represent~~ are, independently, **i)** H, a lower alkyl, or **ii)** lower arylalkyl ;

Z_9 ~~represents a~~ is a lower alkyl or lower arylalkyl ;

Z'_{11}, Z'_{12} and Z'_{13} ~~represent~~ are, independently, a lower alkyl ~~radical~~ ;

	Z_{16}	represents H or $-OZ_{21}$;
	Z_{17}	represents $-OZ'_6$ or $-NZ'_6Z'_7$;
	Z_{18} and Z_{19}	represent, independently, H, halo ;
	Z_{20}	represents H ;
	Z_{21}	represents H, a lower alkyl or $-C(O)(CH_2)_mCH_3$;
	Z_p	represents H or a group corresponding to the formula $-C(O)-A-NZ_{22}Z_{23}$, in which A represents a linear or branched alkylene radical optionally substituted by a radical chosen from the free, esterified or salified hydroxy, halogen, free, esterified or salified carboxy, amino and mono or dialkylamino radicals ;
	Z_{22} and Z_{23}	represent, independently, H or a lower alkyl ;
	m	is an integer comprised between 0 and 6;
	n	is 1 or 2; and
	q	represents an integer from 0 to 2; and
	[N=X]	represents a heterocyclic group with 4 to 7 members, X representing the chain necessary to complete said heterocyclic group and selected from the group constituted by O, CH_2, CH, N and NZ_9 ;

or pharmaceutically acceptable salts of thereof.

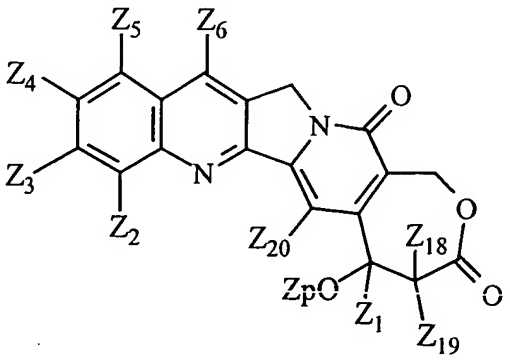
6. Compounds as claimed in any of claims 1 to 5, characterized in that Z_{18}, Z_{19} and Z_{20} represent H ; or pharmaceutically acceptable salts of thereof.

7. Compounds as claimed in any of claims 1 to 6, characterized in that Z_1 represents ethyl or pharmaceutically acceptable salts of thereof.

8. Compounds as claimed in claim 1 or 2, characterized in that Z_p represents a group corresponding to the formula $-C(O)-A-NZ_{22}Z_{23}$ or pharmaceutically acceptable salts of thereof.

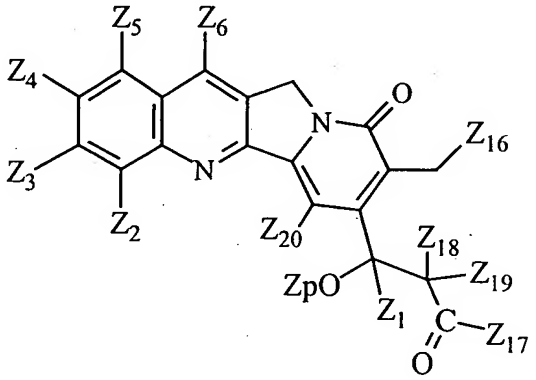
9. Compounds as claimed in claim 1 or 2, characterized in that Z_p represents H or pharmaceutically acceptable salts of thereof.

10. Compounds as claimed in claim 1 or 2, characterized in that they correspond to the formula (AI)



wherein Z_1, Z_2, Z_3, Z_4, Z_5, Z_6, Z_{18}, Z_{19}, Z_{20} and Z_p are as defined in claim 1 ~~,or~~ and a pharmaceutically acceptable salt ~~of~~ thereof.

11. ~~Compounds as claimed in~~ A compound of claim 1 ~~or 2, characterized in that they correspond to~~ shown the formula ~~(A2)~~



wherein Z_1, Z_2, Z_3, Z_4, Z_5, Z_6, Z_{16}, Z_{17}, Z_{18}, Z_{19}, Z_{20} and Z_p are as defined in claim 1 ~~or~~ and a pharmaceutically acceptable salt ~~of~~ thereof.

12. ~~Compounds as claimed in~~ A compound of claim 1 ~~or 2, characterized in that~~ where Z_6 ~~represents~~ is $-(CH_2)_mSiZ'_{11}Z'_{12}Z'_{13}$ and a pharmaceutically acceptable salt ~~of~~ thereof.

13. ~~Compounds as claimed in claim 12, characterized in that they correspond to the following formula~~ A compound of claim 1 selected from the group consisting of :

(5*R*)-5-ethyl-9,10-difluoro-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino[3',4':6,7]indolizino [1,2-*b*] quinoline-3,15-dione ~~and~~

(5*R*)-5-ethyl-5-hydroxy-12-(2-trimethylsilylethyl)-4,5,13,15-tetrahydro-1*H*,3*H*-oxepino [3',4':6,7]indolizino [1,2-*b*] quinoline-3,15-dione ;

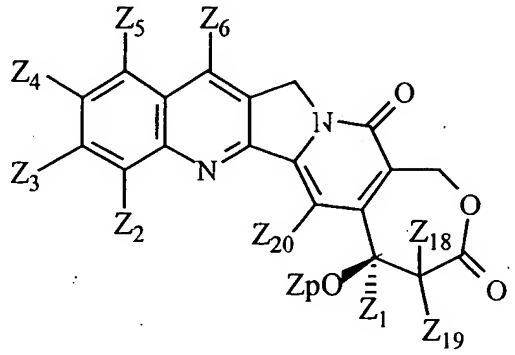
14. ~~Compounds as claimed in~~ A compound of claim 1 ~~or 2, characterized in that~~ where Z_2 ~~represents~~ is H or halo, Z_3 ~~represents~~ is halo, Z_4 ~~represents~~ is H, halo ~~or~~ and lower alkyl, Z_5 ~~represents~~ is H or halo, and Z_6 ~~represents~~ is H, lower alkyl ~~or~~ and $-(CH_2)_n[N=X]$ substituted ~~in which the substituent is a~~ with lower alkyl and a pharmaceutically acceptable salt ~~of~~ thereof.

15. ~~Compounds as claimed in claim 14, characterized in that they correspond to the following formula~~ A compound of claim 1 selected from the group consisting of:

(*5R*)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1H,3H-oxepino [3',4':6,7] indolizino [1,2-b] quinoline-3,15-dione and

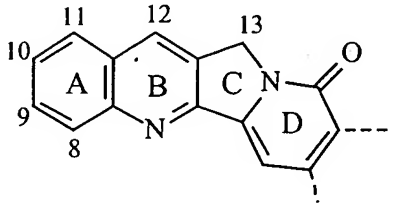
(*5R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1H,3H-oxepino [3',4':6,7] indolizino [1,2-b] quinoline-3,15-dione ; or pharmaceutically acceptable salts of thereof.

16. A ~~Compounds as claimed in~~ claim 1 ~~or 2, characterized in that they correspond to~~ the formula

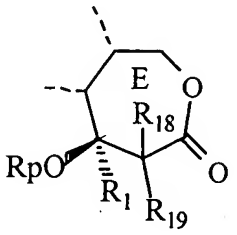


wherein Z_1, Z_2, Z_3, Z_4, Z_5, Z_6, Z_{18}, Z_{19}, Z_{20} and Z_p are as defined in claim 1 and a pharmaceutically acceptable salts thereof.

17. A method of treating cancer in warm-blooded animals comprising administering to warm-blooded animals in need thereof a camptothecin analog characterized in that said analog is a [A,B,C,D,E] pentacyclic compound, the cycles [A,B,C,D]



comprising any substitution on the various sites available for substitution(s), and the [E] cycle being a 7-ring member ß-hydroxy lactone ring of the formula



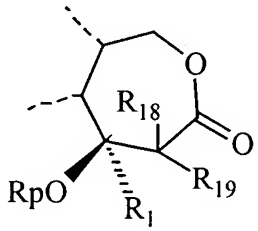
wherein R_1 is selected from the group consisting of alkyl of 1 to 6 carbon atoms, alkenyl and alkynyl of 2 to 6 carbon atoms, haloalkyl of 1 to 6 carbon atoms, alkoxyalkyl of 2 to 12 carbon atoms and alkylthioalkyl of 2 to 12 carbon atoms, R_p is hydrogen or an easily cleavable group, R_{18} and R_{19} are individually selected from the group consisting of hydrogen, halogen, OH and alkyl and alkoxy of 1 to 6 carbon atoms and its non-toxic, pharmaceutically acceptable salts.

18. A method of treating cancer according to claim 17, the cycles [A,B,C,D] comprising any substitution on the sites 8, 9, 10, 11, 12 or 13.

19. A method of treating cancer according to claim 17, the cycles [A,B,C,D] comprising any substitution on the sites 8, 9, 10, 11 or 12.

20. A method of treating cancer according to claim 17, the cycles [A,B,C,D] comprising any substitution on the sites 9, 10, 11 or 12.

21. A method of treating cancer in warm-blooded animals comprising administering to warm-blooded animals in need thereof a camptothecin having 5 rings with a 7-ring member ß-hydroxy lactone ring of the formula



wherein R_1 is selected from the group consisting of alkyl of 1 to 6 carbon atoms, alkenyl and alkynyl of 2 to 6 carbon atoms, haloalkyl of 1 to 6 carbon atoms, alkoxy alkyl of 2 to 12 carbon atoms and alkylthioalkyl of 2 to 12 carbon atoms, R_p is hydrogen or an easily cleavable group, R_{18} and R_{19} are individually selected from the group consisting of hydrogen, halogen, OH and alkyl and alkoxy of 1 to 6 carbon atoms and its non-toxic, pharmaceutically acceptable salts.

22. A method of treating cancer as claimed in claim 17 ~~or 21, characterized in that~~ wherein the cancer is selected from the group consisting of leukemia, colon cancer, lung cancer, prostate cancer, breast cancer, melanoma, ovarian cancer and gastric cancer.

23. A method of treating cancer as claimed in claim 22, ~~characterized in that~~ wherein the cancer is selected from the group consisting of leukemia, colon cancer, lung cancer, prostate cancer and breast cancer.

24. A method ~~as claimed in any of claims 17 to 23 characterized in that~~ wherein R_{18} and R_{19} are hydrogen.

25. A method ~~as claimed in any of claims 17 to 24 characterized in that~~ wherein R_p is hydrogen.

26. A method ~~as claimed in any of claims 17 to 25 characterized in that~~ wherein R_1 is ethyl.

27. A method ~~as claimed in any of claims 17 to 26 characterized in that~~ wherein the camptothecin analog is selected from the group consisting of

(*5R*)-5-ethyl-9,10-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1H,3H-oxepino [3',4':6,7] indolizino [1,2-b] quinoline-3,15-dione ;

(*5R*)-1-[9-chloro-5-ethyl-5-hydroxy-10-methyl-3,15-dioxo-4,5,13,15-tetrahydro -1H,3H-oxepino [3',4:6,7] indolizino [1,2-b] quinolin-12-yl-methyl]-4-methyl-hexahydropyridium chloride ;

(*5R*)-5-ethyl-9,11-difluoro-5-hydroxy-4,5,13,15-tetrahydro-1H,3H-oxepino [3',4':6,7] indolizino [1,2-b] quinoline-3,15-dione and

(*5R*)-5-ethyl-9,11-difluoro-5-hydroxy-12-propyl-4,5,13,15-tetrahydro-1H,3H-oxepino [3',4':6,7] indolizino [1,2-b] quinoline-3,15-dione ~~; or its~~ a pharmaceutically acceptable salt thereof.